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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/539,859	06/17/2005	John Cumming	06275-458US1 100887-1P US	4840
26164 7590 02/08/2008 FISH & RICHARDSON P.C. P.O BOX 1022 MINNEAPOLIS, MN 55440-1022			EXAMINER RAHMANI, NILOOFAR	
			ART UNIT 1625	PAPER NUMBER
			MAIL DATE 02/08/2008	DELIVERY MODE PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

**Office Action Summary**

Application No.

10/539,859

Applicant(s)

CUMMING ET AL.

Examiner

Niloofer Rahmani

Art Unit

1625

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --****Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**1) ☒ Responsive to communication(s) filed on 17 June 2005.2a) ☐ This action is **FINAL**.2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**4) ☒ Claim(s) 1-11 and 14-20 is/are pending in the application.

4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.6) ☒ Claim(s) 1-11, 14-20 is/are rejected.7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.**Application Papers**9) ☐ The specification is objected to by the Examiner.10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.**Priority under 35 U.S.C. § 119**12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).a) ☒ All b) ☐ Some \* c) ☐ None of:1. ☒ Certified copies of the priority documents have been received.2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**1) ☒ Notice of References Cited (PTO-892)2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)3) ☐ Information Disclosure Statement(s) (PTO/SB/08)

Paper No(s)/Mail Date \_\_\_\_\_.

4) ☐ Interview Summary (PTO-413)

Paper No(s)/Mail Date. \_\_\_\_\_.

5) ☐ Notice of Informal Patent Application6) ☐ Other: \_\_\_\_\_.

### DETAILED ACTION

1. Claims 1-11, and 14-20 are currently pending in the instant application and claims 12-13 are cancelled.

#### *Priority*

2. This application is file on 06/17/2005, which is a 371 of PCT/SE03/02008, filed on 12/18/2003, which claims priority of SWEDEN 0203821.4, filed on 12/20/2002, and SWEDEN 0300499-1, filed on 02/24/2003, and SWEDEN 0301425.5, filed on 05/15/2003.

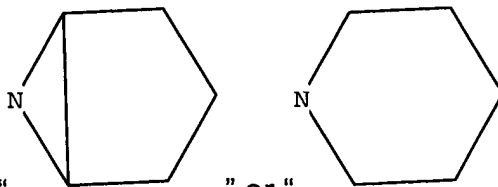
3. ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11, and 14-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-11, and 14-20 are rejected because the term "A" is confusing.



Does applicants mean " " or " "? Correction is required.

4. Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

which applicant regards as the invention. The term "to prepare a compound" is confusing. Which compound is prepared by coupling of formula (III) with formula (IV) in part (a)? And which compound is prepared by coupling of formula (III) with (V) in part (b)? Correction is required.

**5. Claim Rejections - 35 USC § 112**

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11, and 14-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making solvates and hydrates of the claimed compounds. The specification does not enable any person skilled in the art of synthetic organic chemistry to make the invention commensurate in scope with these claims. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. a) Determining if any particular substrate would form a solvate or hydrate would

require synthesis of the substrate and subjecting it to recrystallization with a variety of solvents, temperatures, pressures, and humidity. The experimentation is potentially open-ended. b) The direction concerning the solvates is found on pages 61-62, which simply states Applicants intent to make them. c) There is no working example of any hydrate or solvate formed. The claims are drawn to solvates, yet the numerous examples presented all failed to produce a solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

d) The nature of the invention is chemical synthesis, which involves chemical reactions. e) The state of the art is that is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). West, Anthony R., "Solid State Chemistry and its Applications, Wiley, New York, 1988,

pages 358 & 365. The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is their compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometry of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. In the same paragraph on page 365 West (Solid State Chemistry) explains that it is possible to make meta-stable non-equilibrium solvates, further clouding what Applicants mean by the word solvate. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stable region of the solvate. f) The artisan using Applicants invention to prepare the claimed compounds would be a process chemist or pilot plant operator with a BS degree in chemistry and several years of experience. g) Chemical reactions are well-known to be unpredictable, *In re Marzocchi*, 169 USPQ 367, *In re Fisher*, 166 USPQ 18. h) The breadth of the claims includes all of the thousands of compounds of formula (I) as well as the presently unknown list of solvents embraced by the term "solvate".

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art

how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

**6. Claim Rejections - 35 USC § 112**

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 14 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the

disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

- 1) The breadth of the claims.
- 2) The nature of the invention,
- 3) The state of the prior art,
- 4) The level of one of ordinary skill,
- 5) The level of predictability in the art,
- 6) The amount of direction provided by the inventor,
- 7) The existence of working examples,
- 8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

**The nature of the invention:** The instant invention is drawn to a method of treating a CCR5 mediated disease state comprising administering to a patient in need of such treatment an effective amount of a compound as claimed in claim 1.

**The state of the prior art:** " The internalization of the receptors CCR1 and CCR5 that mediate arrest and transmigration of these cells in response to RANTES was prevented by vMIP-II, supporting its role as an antagonist of CCR1 and CCR5. Thus, our data provide evidence for a immunomodulatory role of vMIP-II in directing inflammatory cell recruitment away from a Th1-type towards a Th2-type response and thereby facilitating evasion from cytotoxic reactions."(Weber et al., European Journal of Immunology, Vol. 31(8), 2001,pages 2458-2466).



The state of the prior art is that it involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seeming high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

**The predictability in the art:** It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to the therapeutic effects, whether or not the compounds of formula of claim 1 would be useful for treating a pharmacological condition in a subject.

**Amount of guidance/working examples:** On page 94 of the specification, applicants have examples claimed compounds and Pic50 activity. Applicant provides no guidance for how to treat a CCR5 mediated disease. There are no examples in the instant specification showing that the instant compounds can treat CCR5 mediated disease. Nor are there any examples of the diseases being either treated by CCR5 mediated.

**The breadth of the claims:** The breadth of claims is drawn to a method of treating a CCR5 mediated disease state comprising administering to a patient in need of such treatment an effective amount of a compound as claimed in claim 1.

**The quantity of undue experimentation needed:** Since the guidance and teaching provided by the specification is insufficient for treating a mammal having a CCR5 mediated disease using the compound of claim 1, one of ordinary skill in the art, even with high level of skill, is unable to use the instant compounds as claimed without undue experimentation.

**The level of the skill in the art:** The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Taking all of the above into consideration, it is not seen where the instant claim 14, for treating a mammal having a CCR5 mediated disease using the compound of claim 1, have been enabled by the instant specification.

**7. *Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

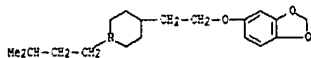
(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1,4-8, and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Brown et al. WO 9202502. Brown et al. disclosed the instant claimed compound and composition, which from the STN search is

**RN** 141430-03-7

**CN** Piperidine, 4-[2-(1,3-benzodioxol-5-yloxy)ethyl]-1-(3-methylbutyl)-, hydrochloride



• 821

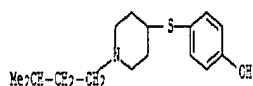
and

composition on abstract. Therefore, the instant claim is anticipated by Brown et al.

8. Claims 1,4-8, and 11 are rejected under 35 U.S.C. 102(e) as being anticipated by Astles et al. US 20050070520. Astles et al. disclosed the instant claimed compound and composition, which from the STN search is

**RN** 569660-26-0

**CN** Phenol, 4-[[1-(3-methylbutyl)-4-piperidiny]thio]



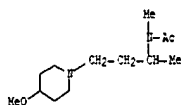
and

composition on abstract. Therefore, the instant claim is anticipated by Astles et al.

9. Claims 1,4-8, and 11 are rejected under 35 U.S.C. 102(a) as being anticipated by Tang et al., Zhongguo Jishui Paishui, 2002, 18(7), pages 5-7. Tang et al. disclosed the instant claimed compound, which from the STN search is

**RN** 677731-37-2

**CN** Acetamide, N-[3-(4-methoxy-1-piperidiny)-1-methylpropyl]-N-methyl-

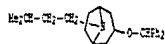


Therefore, the instant claim is anticipated by Tang et al.

10. Claims 1,4-8, and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Boehringer et al., DE 1077223. Boehringer et al. disclosed the instant claimed compound, which from the STN search is

**RN** 102953-94-6

**CN** Nortropane, 3-diphenylmethoxy-8-isopentyl-, hydrobromide



• • •

. Therefore, the instant

claim is anticipated by Boehringer et al.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Niloofar Rahmani whose telephone number is 571-272-4329. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

NILOOFAR RAHMANI

01/31/2008

NA

A handwritten signature in black ink, appearing to read 'Margaret D. Seaman'.

MARGARET D. SEAMAN

PRIMARY EXAMINER

GROUP 1625